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UINTENDENCIA DE INDUSTRIA V COMERCIO

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

- Re: Expecliente No. 05.102.278
Solicitud de patente a nombre de NOVARTIS AG. Y MITSUBISHI PHARMA CORPORATION

Yo, DILIA 1\’LRIA RODRIGUEZ D’ALEMAN, actuando como apoderada sustituta de acuerdo con la sustitución presentada el 2 de junio de 2009, identificada como aparece al pie de mi firma, domiciliada en la carrera 11 A No. 86-53, piso 6, obrando como apoderada de la sociedad NOVARTIS AG. Y MITSUBISHI PHARMA CORPORATION, domiciliada en Basilea Suiza, y Osaka Japon, solicitante de la patente de la referencia, dando alcance a nuestra respuesta del 8 de enero de 2009 con la cual se dio respuesta al oficio No. 11663 notificado por fijación en lista el 12 de septiembre de 2008 relacionado con ci concepto tØcnico de fondo No. 2510, me permito manifestar:

1. Con fundamento en la facultad que confiere ci artIculo 34 de la Decision
486 al solicitante para modificar la solicitud de patente en cualquier momento del trÆmite, presento junto con este memorial nuevo capItulo reivindicatorio que consta de 31 reivrndicaciones que reempiaza aquel presentado ci 8 de enero de
2009 para la solicitud orna1T en ci cual se realizaron las siguientes
moclificaciones:

1.1 Se especificó dentro de la antigua reivindicación 1 la naturaleza del
agonista del receptor del SIP, de tal forma que se limitc ci agonista del SiP dentro dc la composición oral sólida a los compuestos dc formula M.

En este senudo, atentamente nos permitimos presentar la siguicnte tabla que mucstra ci sustento para cada una dc las reivindicaciones de la solicitud original.

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Nueva

relvinificaclon Sustento
1 PÆgina2, linea 19 pÆgina 16,lineas 6 a 11 de la memoria
descriptiva.
2 PÆgina2, linea 19 pÆgina 16,lineas 6 a 11 los ejemplos,
principalmente el ejemplo 1, pÆgina 28 29 de la memoria descriptiva.
3 PÆgina2, lIneas 14 15 el ejemplo 6 en la pÆgina 31 de lit
memoria descriptiva.
4 PÆgina 20 entrelas lineas 7 8 de la memoria descriptiva.
5 PÆgina20 desde la linea 21 hasta la pÆgina 21 linea 3 de la
descripción.
6 PÆgina 20 desde la linea 21 hasta la pÆgina 21 linea 3 de la
descripción.
7 Nina 20 desde la linea 21 hasta la linea 10 de la
descripción.
8 PÆgina 20 desde la linea 21 hasta la pÆgina21 linea 3 de la
descripción.
9 PÆgina 20 desde la linea 7 hasta Lalinea 10 de La descripción.
10 PÆgina 20 lineas21 a 23.
11 PÆgina 19 linea 24 hasta La pÆgina 25 linea 6 de la
descnpción.
12 PÆgina 19 linea 24 hasta la pÆgina 25 linea 6 de la
descripción.
13 PÆgina 20, lineas 17 a 20 ejemplos 1 a 22 de la
descripción.
14 PÆgina 31 linea 9 a 19 Ejemplo 6a de La memoria
descripuva.
15 PÆgina24, lineas 14 a 25 de la descripción.
16 PÆgina 25, lineas 15 a 19 de ladescripción.
17 PÆgina 21,lineas 8 a 24 pIgina 36, linea 6 de la memoria
descriptiva.
18 PÆgina 21, lineas 8 a 24 pÆgina 36, linea6 de la memoria
descriptiva.
19 PÆgina 21, lIneas 8 a24 pÆgina 36, linea 6 de la memoria
descriptiva.
20 PÆgina 19,lineas 20 a 23 de la descripción.
21 PÆgina19, lIneas 20 a 23 de la descripción.
22 PÆgina21 desde la linea 4 hasta la linea 7 de la descripción.
23 PÆgina 21 desdelit linea 4 hasta la linea 7 de la descripción.
24 PÆgina 21 desde la linea 21 hasta la linea 24 de la
descripción.

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25 PÆgina 21 desde La linea 21 hasta la linea 24 de la
descripción.
26 PÆgina22, linea 25 hasta la pÆgina 23,linea 4 de hi memoria
descriptiva.
27 PÆgina 23, lineas9 a 11 de la descripción.
28 PÆgina 22, linea25 hasta la pÆgina 23, linea 4 de lamemoria
descriptiva.
29 PÆgina 23lineas 1 a 3 ejemplos 28 a 31 de la pÆgina
30 PÆgina 2, linea 19 pÆgina 16, lineas 6 a 11, pÆgma 20,
lineas 21 a 23 de la memoria descriptiva.
31 PÆgina 2, linea 19 pÆgina 16, lineas 6 a 11 pÆgina 16,
lineas 6 a 11 los ejemplos, principalmente ci ejemplo 1,
pÆga28y29 de la memoria descriptiva.

Sobre este particular, nos permitimos manifestar que ci nuevo capItulo reivindicatorio no amplia la materia objeto de la presente invención y se presenta con el fin de especificar las modalidades preferidas de la invención parental en tØrrninos del antagonista del receptor de SiP.

Para este efecto, me permito acompaæar ci recibo con nümero: 09-69,136 del 15 de septiembre de 2009 con el cual queda cubierta la tasa correspondicntc a la modificación en cuanto al capItulo reivindicatorio de la solicitud original.

Habiendo atendido cabalmente las objeciones presentadas pot ese dcspacho a traves del presente escrito y de nuestra respuesta del 8 de enero de 2009 con la cual se clio contestación al oflcio No. 11663 notificado por fljación en lista ci 12 de septiembre de 2008 relacionado con ci concepto tØcnico dc fondo No. 2510, atentamente solicitamos se conceda ci privilcgio de patcnte dc invención a la solicitud original y a la solicitud divisional en estudio o si ci cxaminador considcra que subsisten razones para objetar la presente familia de invcnciones, rogamos expedir otro examen de fondo con los debidos motivos y razoncs que sustcnten su objeción con ci fin de que nuestro mandante tenga la posibilidad de exponcr sus argumentos con base en la interpretación de los artIculos 45 dc hi Decision 486 -el cual otorga la facultad al examinador para emitir los exÆmcncsde fondo-, 35 y 59 del Código Contencioso Administrativo que scæaia que: "habie’ndose dado oportunidad a los interesadospara expresar sus opiniones,j con base en laspruebas e informes di.rponibles, se tornard la decision que serÆ motivada al menos en forma sumaria si afecta a particulares" y "(.) deberÆ proferirseLi decision definiliva. Esta se motivarÆen sus aspectos de hechoji de clerecho,j en los de conveniencia si es el caso ’ respectivamente (El subrayado
es nuestro).

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FORMULARIO LJNICO DE CORRECCIONES Y MODIFICACIONES

SOLICITUD DE:
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Corrección de error material Modilicaciôn a una solicitud. El

2 Nombre: NOVARTIS AG Y MITSUBISHI IDENTIFLCACIÔN
PHARMA CORPORATION
Dirección: Lichtstrasse 35, CH-4002 Basilea, C.C. NIT
SOLICITANTE Suiza Y 6-0 Hiranomachi 2-Chome, Chuo-ku,

(71) Osaka 541-0046 JapOn G.E. Otro El

Nacionalidad o domicillo: Basilea, Suiza
Osaka, Japón Cual
ar de Constitución: Suiza Japôn
Nümero
TelØfono: Fax:
E-mail

3 Nombre: DILIA MARIA RODRIGUEZ IDENTIFICACIÔN
D’ALEMAN

REPRESENTANTE Direcciôn: Carrera 11 No. 86-53, piso 6 CC. NIT
o APODERADO

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Cual
E-mail: cIarkemodetclarkemodet.com.co NUmero 41.654.882
______________________________________ I TP20824_CSJ

4 Nümero del expediente: 05.102278

Descripciôn de la corrección o modificación solicitada: Que se anote: Nuevo Capitulo
4vindicatorio

Comprobante de pago No. 09-69,136

7 Anexos:

Comprobante de pago de la tasa

Poderes si fuese el caso

ElDocumento que acredita la existencia representaciôn legal de las partes, cuando sean personas juridicas.

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424 Mannitol

gloves, and a dust respirator arc recommended. When heated to decomposition, maltose emits acrid smoke and irritating fumes.

16 Regulatory Status

In the USA, maltose is considered as a food by the FDA and is therefore not subject to food additive and GRAS regulations. Included in the FDA Inactive Ingredients Database (oral solutions). Included in the Canadian List of Acceptable Non-medicinal Ingredients. Included in parenteral products available in a number of countries worldwide.

17 Related Substances

Glucose, liquid.

18 Comments

Crystalline maltose. e.g. Advantose 100 (SPI Pharma Group), is spray-dried to produce spherical particles with good flow proper-ties. The material is also nonhygroscopic and is highly compressible. A specification for maltose syrup powder is contained in the apanese Pharmaceutical Excipients cJPE).7 The EINECS number for maltose is 200-716-5. The PubChem Compound D (CD) for maltose includes 6255 and 23724983.

11 Mannitol

1 Nonproprietary Names
BP: Mannitol
JP: D-Mannitol
PhEur: Mannitol
USP: Mannitol

Synonyms

Cordycepic acid; C PharinMannidex; E421; Emprove; manna sugar; n-mannite; mannite; mannitolum; Mannogem; Pearlitol.

3 Chemical Name and CAS Registry Number

’Iannitol [69-65-8)

4 Empirical Formula and Molecular Weight
C6H1406 182.17

5 Structural Formula

OH OH

HO

OH

5H OH

19 Specific References

1 SPI Pharma Group. Technical literature: Advantose 100 maltose, 2004. 14
2 Bowe XE et al. Crystalline maltose: a direct compression pharmaceu-
tical excipient. Pharm Technol Eur 1998; 10(5): 40.
3 Mulderrig KB. Placebo evaluation of selected sugar-based excipients in
pharmaceutical and nutraceutical tableting. Phar,n Technol 2000;
24(5): 34, 36, 38, 40, 42, 44.
4 Palevsky PM et al. Maltose-induced hyponatremia. Ann Intern Med
1993; 118(7):526-528.
S Mundt S, Wedzicha BL. Role of glucose in the Maillard browning of
maltose and glycine: a radiochemical approach. I Agrie Food Chem 2005;53:6798-6803.
6 Lewis RJ, ed. Sax’s Dangerous Properties ofIndustrial Materials, 11th
cdn. New York: Wiley, 2004; 2275.
7 Japan Pharmaceutical Excipients Council. Japan Pharmaceutical Excipients, 2004. Tokyo, Yakuji Nippo: 2004; 516-518.

20 General References

21 Author

CK Tye.

22 Date of Revision

19 February 2009.

6 Functional Category

Diluent plasticizer; sweetening agent; tablet and capsule diluent; therapeutic agent; tonicity agent.

7 Applications in Pharmaceutical Formulation or
Technology

Mannitol is widely used in pharmaceutical formulations and food products. In pharmaceutical preparations it is primarily used as a diluent (10-90% w/w) in tablet formulations, where it is of particular value since it is not hygroscopic and may thus be used with moisture-sensitive active ingredients. 1.2)
Mannitol may be used in direct-compression tablet applica-tions,341 for which the granular and spray-dried forms are available, or in wet granulations. (5,6) Granulations containing mannitol have the advantage of being dried easily. Specific tablet applications include antacid preparations, glyceryl trinitrate tablets, and vitamin preparations. Mannitol is commonly used as an excipient in the manufacture of chewable tablet formulations because of its negative heat of solution, sweetness, and ’mouth
feel’.6’7

In lyophilized preparations, mannitol (20-90% w/w) has been included as a carrier to produce a stiff, homogeneous cake that improves the appearance of the lyophilized plug in a vial.810 A pyrogen-free form is available specifically for this use.
Mannitol has also been used to prevent thickening in aqueous antacid suspensions of aluminum hydroxide (<7% w/v). It has been suggested as a plasticizer in soft-gelatin capsules, as a component of sustained-release tablet formulations,(] and as a carrier in dry powder inhalers.12’3 It is also used as a diluent in rapidly

Mannitol 425,.1

dispersing oral dosage forms, 114,15) It is used in food applications as a hulking agent.
Therapeutically, mannitol administered parenterally is used as an osmotic diuretic, as a diagnostic agent for kidney function, as an adjunct in the treatment of acute renal failure, and as an agent to reduce intracranial pressure, treat cerebral edema, and reduce intraocular pressure. Given orally, mannitol is not absorbed significantly from the gastrointestinal tract, but in large doses it can cause osmotic diarrhea; Section 14.

8 Description

Mannitol is D.manflitol. It is a hexahydric alcohol related to mannose and is isomeric with sorbitol.
Mannirol occurs as a white, odorless, crystalline powder, or free-flowing granules. It has a sweet taste, approximately as sweet as glucose and half as sweet as sucrose, and imparts a cooling sensation in the mouth. Microscopically, it appears as orthorhom-bic needles when crystallized from alcohol. Mannitol shows polymorphism. (16)

9 Pharmacopeial Specifications
See Table 1. See also Section 18.

SEM 1: Excipient: mannitol: manufacturer: Merck; magnification: 50x; voltage: 3.5 kV

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SM 2: Excipient; mannitol; manufacturer: Merck; magnification: 500x; voltage: 3.5kv.

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SEM 3: Excipient: mannitol powder; manufacturer: SPI Polyols Inc.; lot no: 3140G8; magnification: lOOx.

SEM 4: Excipient: mannitol granular; manufacturer: SPI Polyols Inc.; lot no: 2034F8; magnification: lOOx.

10 Typical Properties
Compressibility Figure 1.
Density (bulk)
0.430 g/cm3 for powder;
0.7 g/cm3 for granules.
Density (tapped)
0.734 g/cm3 for powder;
0.8 g/cm3 for granules.
Density (true) 1.5 14 glcm3
Dissociation constant PKa = 13.5 at 18°C
Flash point <150°C
Flowability Powder is cohesive, granules are free flowing.

Heat ofcombustion 16.57kJ/g (3.96 kcallg) Heatofsolution 120.9J/g (-28.9callg) at 25°C
Melting point 166-168°C
Moisture content see Figure 2.
NIR spectra see Figure 3.
Osnzolarity A 5.07% wlv aqueous solution is isoosmotic with
serum.

Particle size distribution

Pearlitol 300 DC: maximum of 0.1% greater than 500 pm and minimum of 90% greater than 200 lam in size;

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426 Mannitol

Test iF XV PhEur 6.4 USP 32

Identification
Characters
Appearance of
solution
Melting range 166-169C 165-170°C
Specific rotation -137’ to +145’ +23 to +25
Conductivity 20i.tS.cm
Acidity
Loss on drying 0.3%
Chloride s0.007%
Sulfate 0.01%
Arsenic 1.3 ppm
Lead 0.5 ppm
Nickel 1 ppm
Heavy metals 5 ppm
Reducing sugars
Residue on 0.10%
ignition
Related
substances

acteri&- 4IU/gM

endotoxinst°1

2.5 lU/g
Microbial 100cFu/g
contamination
Assay (dried 98.0% 98.0-102.0%
basis)

164-169°C
+137°to+145°

0.007%
0.01%
1 ppm

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Compression force (kN)

Figure 1: Compression characteristics of granular mannitol (Pearlitol, - Rpquette FrŁres).
V Tablet diameter: 20 mm. Lubricant: magnesium steorote0.7% w/w for
96.0-101.5% Pearlitol 400 DC and Pearlitol 500 DC; magnesium stearaiT% w/w For Pearlitol 300 DC. --

(0) Test applied only if the mannitol is to be used In the manufacture of parenteral sage rot Ms.
))For porenteral preparations having a concentration of lOOg/L or less of mannitol. -1 For parental preparations having a concentration of more than 100 gIL of mannitol.

)-

Pearl/to! 400 DC: maximum of 20% greater than 500 pm and minimum of 85% greater than 100 im in size; cc

Pearlitci! 500 DC: maximum of 0.5% greater than 841 p.m and minimum of 90% greater than 150 l.Im in size.
Average particle diameter is 250 lam for Pearlitol 300 DC,
360 l.trn for Pearlitol 400 DC and 520 pm for Pearlitol 500 DC. ’l See also Figure 4.
Refractive index nD.O = 1.333
Solubility see Table U.
/’°’.pecific suiface area 0.37-0.39 m2/g

ToWe U.- Solubility of

Solvent Solubility at 20°C
Alkalis Soluble
Ethanol (95%) 1 in 83
Ether Practically insoluble
ycerin 1 in 18
pan.2-ol 1 in 100
Woter 1 in 5.5

11 Stability and Storage Conditions

Mannirol is stable in the dry state and in aqueous solutions. Solutions may be sterilized by filtration or by autoclaving and if necessary may he autoclaved repeatedly with no adverse physical or chemical effects.118t In solution, mannitol is not attacked by cold, dilute acids or alkalis, nor by atmospheric oxygen in the absence of catalysts. Mannitol does not undergo Maillard reactions.
The bulk material should be stored in a well-closed container in a cool, dry place.

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Sorption equilibrium moisture
Desorption equilibrium moisture

33 43 52 57 67 75 100

Relative humidity (%)

Figure 2: Sorptiondesorption isotherm For mannitol.

12 Incompatibilities

Mannitol solutions, 20% w/v or stronger, may be salted out by potassium chloride or sodium chloride. 19) Precipitation has been reported to occur when a 25% w/v mannitol solution was allowed

to contact plastic. 120) Sodium cephapirin at 2 mg/mL and 30 mg/mL concentration is incompatible with 20% w/v aqueous mannitol solution. Mannitol is incompatible with xylitol infusion and may form complexes with some metals such as aluminum, copper, and iron. Reducing sugar impurities in mannitol have been implicated in the oxidative degradation of a peptide in a lyophilized forma-
tion.t21 Mannitol was found to reduce the oral bioavailability of
cimetidine compared to sucrose.

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Mannitol 427

2245

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68

1674

. 1498 1636 .’2168 2123 2452

2082 2261
I I I I I I I I I . -0.2
1100 1300 1500 1700 1900 2100 2300 2500

Wavelength/nm

Figure 3 Near-infrared spectrum of mannitol measured by reflectance. UKI

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Particle diameter (pm)

Figure 4: Particle size distribution of monnitol powder.

13 Method of Manufacture

Mannitol may he extracted from the dried sap of manna and other natural sources by means of hot alcohol or other selective solvents. It is commercially produced by the catalytic or electrolytic reduction of monosaccharides such as mannose and glucose.

14 Safety

Mannitol is a naturally occurring sugar alcohol found in animals ’and plants; it is present in small quantities in almost all vegetables. Laxative effects may occur if mannitol is consumed orally in large quantities. 12_1 If it is used in foods as a bodying agent and daily ingestion of over 20 g is foreseeable, the product label should bear the statement excessive consumption may have a laxative effect’. After intravenous injection, mannitol is not metabolized to any appreciable extent and is minimally reabsorbed by the renal tubule, about 80% of a dose being excreted in the urine in 3 hours.(24) A number of adverse reactions to mannitol have been reported, primarily following the therapeutic use of 20% w/v aqueous intravenous infusions. 51 The quantity of mannitol used as an excipient is considerably less than that used therapeutically and is consequently associated with a lower incidence of adverse reactions. However, allergic, hypersensitive-type reactions may occur when mannitol is used as an excipient.

An acceptable daily intake of mannitol has not been specified by
the WHO since the amount consumed as a sweetening agent was
not considered to represent a hazard to health.1261 10
LDso (mouse, IP): 14 g/kg127
LD50 (mouse, IV): 7.47 g/kg
LD50 (mouse, oral): 22 g/kg
LD50 (rat, IV): 9.69 g/kg
LD50 (rat, oral): 13.5 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Mannitol may be irritant to the eyes; eye protection is recommended.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (!P, IM, TV, and SC injections; infusions; buccal, oral and sublingual tablets, powders and capsules; ophthalmic preparations; topical solutions). Included in nonparenteral and parenreral medicines licensed in the UK. Included in the Canadian List of Acceptable Mon-medicinal Ingredients.

17 Related Substances

Sorbitol.

18 Comments

Mannitol is one of the materials that have been selected for harmonization by the Pharmacopeial Discussion Group. For further information see the General Information Chapter <1196> in the USP32-NF27, the General Chapter 5.8 in PhEur 6.0, along with the State of Work’ document on the PhEur EDQM website, and also the General Information Chapter 8 in the JP XV
Mannitol is an isomer of sorbitol, the differnceberweenthetwo polyols occurring in the planar orientation of the grppp on the suliitid chrbitom. Each isomer is characterized by its own individual set of properties, the most important difference being the response to moisture. Sorbitol is hygroscopic, while mannitol-resists moisture sorption, even at high relative humidities.
Granular mannitol flows well and imparts improved flow properties to other materials. However, it usually cannot be used with concentrations of other materials exceeding 25% by weight. Recommended levels of lubricant are I % w/w calcium stearate or 1-2% w/w magnesium stearate. Suitable binders for preparing granulations of powdered mannitol are gelatin, methylcdllulose 400, starch paste, povidone, and sorbitol. Usually, 3-6 times as much magnesium stearate or 1.5-3 times as much calcium stearate is needed for lubrication of mannitol granulations than is needed for other excipients.
A study has examined the influence of common cxcipients such as sucrose and trehalose, on the crystallization of mannitol in freeze-drying.12 -

Mannitol has been reported to sublime at 130°C.1291
Ludifla-sh (BASF) is a coprocessed excipient used as a tablet filler, binder, and disintegrant, and contains mainly mannitol, and also crospovidone and polyvinyl acetate.
A specification for mannitol is contained in the Food Chemicals Codex (FCC).130
The EINECS number for mannitol is 200-711-8. The PubChem Compound ID (CID) for mannitol includes 6251 and 453.

19 Specific References
Allen IV. Featured excipient: capsule and tablet diluents. mt J Pharm Compound 2000; 4(4): 306-310324-325.

Europªlsches Patentamt

(19) j European Patent Office

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Chlkujo-gun, Fukuoka 871-8550 (JP)
(30) Priority: 19.01.1998 JP 804598 MISHINA, Tadashi,
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BahnhotsvorpIa 1 (Delchmannhaus)
50667 KôIn (DE)

(54) MEDICINAL COMPOSITIONS

(57) The present invention provides a pharmaceuti-
cal cori’position containing 2-amino-2-[2-(4-octylphe-
nyl)ethyl]propane-1,3-diol or a pharmaceutically acceptable acid addition salt thereof, and cyclodextrin as astabillzer, and where necessary, saccharlde, which can be prepared into a liquid agent, and which is useful for the suppression of rejection in organ or bone marrow transplantation, immunosuppressive sustention therapy therefor or the treatment of autoimmune diseases.

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ems simultaneously by the incorporation of cyclodextrin as a stabilizer along with 2-amlno-2-[2-(4-octylphenyl)ethylpropane-1,3-dioI or a pharmaceutically acceptable acid addition salt thereof, and Is particularly char-acterized in that It provides a liquid agent superior In detoaming performance and tree from crystal precipitation of the active Ingredient compound. In the present Invention, it has been also found that the Incorporation of a saccharlde selected from monosaccharides, disaccharides and sugar alcohols results in a liquid composition further Improved In local Irritation.

[0010] The pharmaceutical composition of the present Invention contains 2-amlno-2-[2-(4-octyiphenyl)ethypro-
pane-1,3-dlol or a pharmaceutically acceptable acid addition salt thereof as an active ingredient and cyclodextrin as a stabilizer, and where desired, a saccharide.
10 [0011] The present invention also provides use of cyclodextrin for the preparation of a pharmaceutical composition
containing cyclodextrin, wherein crystal precipitation of the active Ingredient compound has been Inhibited, an inhibitor
of crystal precipitation of the active ingredient compound In a pharmaceutical composition containing cyclodextrin, and
a medical agent wherein crystal precipitation of the active ingredient compound In a pharmaceutical composition has been Inhibited.
15 [0012] The 2-amino-2-[2-(4-octyiphenyl)ethyl]propane-1,3-diol and a pharmaceutically acceptable acid addition
salt thereof, that are the active Ingredients of the pharmaceutical composition of the present invention, can be produced according to the method described in W094108943. Preferred compound Is 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride. As other acid addition salts, there are exemplified hydrobromide, sulfate, acetate, fumarate, maleate, benzoate, citrate, malate, methanesulfonate, benzenesulfonate and the like.
20 [0013] The 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol or a pharmaceutically acceptable acid addition salt
thereof is added in a proportion of 0.01 -20 wt%, particularly preferably 0.1 - 10 wt%, of the total weight of the compo-sition.

[0014] The cyclodextrin to be used In the present invention is naturally occurring cyclodextrin, branched cyclodex-
trin, alkyl cyclodextrin or hydroxyalkyl cyclodextrin. Specifically exemplified are a-cyclodextrin (e.g., trademark: Cerdex
25 A-100 manufactured by Nihon Shokuhin Kako Co., Ltd.), -cyclodextrin (e.g., trademark: Cerdex B-1 00 manufactured
by Nihon Shokuhin Kako Co., Ltd.), y-cyclodextrin (e.g., trademark: Cerdex G-100 manufactured by Nihon Shokuhin Kako Co., Ltd.), dodecakis-2,6-0-methyl-a-cyclodextrin, tetradecakis-2,6-0-methyl-3-cyclodextrIn, hexadecakis-2,6-0-methyl-y-cyclodextrin, tetradecakls-2,6-0-ethyl-13-cyclodextrin, a-cyclodextrin partially etherified with 2-hydroxypropyl, -cyclodextrin partially etherifled with 2-hydroxypropyl (HP--CyD, e.g., trademark: Cerdex HP-j3-CD manufactured by
30 Nihon Shokuhin Kako Co., Ltd.), branched a-cyclodextrin and branched0-cyclodextrin wherein glucose and maltose
have been bonded via cz-1,6-glucoside bond, and the like. These cyclodextrins are added in an amount of 1-50 parts by weight, particularly preferably 10-30 parts by weight, per part by weight of the above-mentioned active ingredient
[0015] The saccharide to be used in the present invention is selected from monosaccharides, disaccharides and
sugar alcohols, and is exemplified by glucose, fructose, D-maltose, lactose, sucrose, D-mannitol, D-xylitoi and D-sorb-
35 Itoh which may be used alone or in combination. These saccharides are added In an amount of 1-100 parts by weight,
particularly preferably 5-80 parts by weight, per part by weight of 2-amino-2-[2-(4-octylphenyl)ethypropane-1,3-diol or
a pharmaceutically acceptable acid addition salt thereof.
(0016] When 2-amino-2-[2-(4-octylphenyi)ethyl]propane-1,3-diol or a pharmaceutically acceptable acid addition
salt thereof (particularly hydrochloride) Is prepared into an aqueous solution, It foams at a concentration of 0.01 20
40 wt%, and causes hemolysis and local irritation. The present compound shows special dissolution mechanism wherein,
when it is prepared into an aqueous solution having a concentration higher than 0.1 wt%, it is dissolved after forming micelle, and at a concentration lower than 0.05 wt%, it is dissolved to give a solution without forming micelle. As a result
of this unique dissolution mechanism, crystals are precipitated in an aqueous solution having a concentration of 0.05 - 0.1 wt%. The incorporation of cyclodextrin Into the aqueous solution enables inhibition of the precipitation of crystals
45 due to the formation of micelle, as well as simultaneous resolution of the problems of foaming, hemolysls and local irri-
tation, which characterizes the present invention.
[0017] The pharmaceutical composition of the present Invention takes the preparation form of a liquid agent, which
may be injection, eye drop, nose drop, ear drop, infusion, liquid for oral administration, liquid for inhalation, liquid for lotion and the like, with preference given to injection (intravenous, subcutaneous, intramuscular, etc.) eye drop and infu-
50 sion. These preparation forms are appropriately selected according to the diseases to be treated, conditions thereof,
sex and age of patient, application site and the like, and the preparation is formulated by a method known to those of ordinary skill in the art.
[0018] The pharmaceutical composition of the present Invention can be placed In the market as a completed liquid
preparation, or as a kit Including a powder or iyophillzed product containing the active Ingredient etc. and a liquid for
55 dissolution. For example, the active ingredient, 2-amino-2-[2-(4-octylphenyl)ethyi]propane-1,3-dlol or a pharmaceuti-
cally acceptable acid addition salt thereof (particularly hydrochloride) is dissolved in purified water and the resulting solution is sterilized by filtration, filled In vials and freeze-dried in vacuo to give lyophilized products. As a liquid for dis-solution, an aqueous solution is prepared by dissolving cyclodextrin to be used in the present Invention and, where nec-

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’ essary, saccharide, in distilled water. The aforementioned lyophilized product can be dissolved In the liquid for
dissolution when in use. The liquid for dissolution is used in a 5-fold to 2000-fold amount (parts by weight) relative to the amount of 2-amino-2.[2-(4-octylphenyl)ethy propane-1,3-dlol or a pharmaceutically acceptable acid addition salt thereof. As used herein, the distilled water Is preferably distilled water for injection In the case of an injection. The afore-mentioned lyophlllzed product Is generally filled In vials, and after displacement with nitrogen, applied with a rubber stopper and sealed with aluminum, after which the product can be stored for a long time at room temperature. The cyclodextrin and saccharlde to be further added where necessary can be contained in the lyophilized product together with the active ingredient, 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-dlol or a pharmaceutically acceptable acid addition salt thereof, rather than in the liquid for dissolution as mentioned above. The cyclodextrin Is added In an amount
10 of 1 50 parts by weight, particularly preferably 10 - 30 parts by weight, per part by weight of the above-mentioned
active ingredient. The saccharide to be further added where necessary is added In an amount of 1 100 parts by weight, particularly preferably 5 - 80 parts by weight, per part by weight of the above-mentioned active ingredient.
[0019] The pharmaceutical composition of the present invention may appropriately contain, besides the above-
mentioned ingredients, solubilizer, isotoniclty agent, pH adjusting agent, buffer, antioxidant, thickener, surfactant, pre-
15 servative, humectant, aromatic, coloring agent and the like. These additives may be added when formulating the phar-
maceutical composition of the present invention Into a preparation or may be added to the liquid for dissolution in the
kit preparation for dissolution when in use.
[0020] The pharmaceutical composition of the present invention can be used for the suppression of rejection after
organ or bone marrow transplantation, Immunosuppressive sustentlon therapy therefor or the treatment of the diseases
20 of the eye such as Behçets disease, uveltis and the like, dermatitis inclusive of psoriasis, atopic dermatitis, contact der-
matitis and allergic dermatitis, and the like. More particularly, the pharmaceutical preparation of the present invention
can be used for the prophylaxis and treatment of various applicable symptoms conventionally performed with oral prep-arations, such as for lmmunosuppresslon in organ or bone marrow transplantation, various autoimmune diseases, var-
ious allergic diseases and the like.
25 [0021] Accordingly, the composition of the present invention can be used as a liquid agent for the prophylaxis and
treatment of resistance or rejection in organ or tissue transplantation (e.g., transplantation inclusive of allograft of heart,
4 kidney, liver, lung, bone marrow, cornea, pancreas, small bowel, limb, muscle, nerve, fatty marrow, duodenum, skin,
pancreatic Islet cell etc.), graft-versus-host (GvH) disease in bone marrow or small bowel transplantation, autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus eryt1ematosus, nephrotic syndrome lupus, Hashimoto’s thyroiditis,
30 multiple sclerosis, myasthenla gravis, type I diabetes mellitus, type II adult onset diabetes mellitus, uveltis, nephrotic
syndrome, stroid-dependent and steroid-resistant nephrosis, palmoplantar pustulosis, allergic encephalomyelitis, glomerulonephritls etc.), and infectious diseases caused by pathogenic microorganisms. The composition of the
present Invention can be also used for the treatment of the onset of Inflammatory, proliferative and ultraproliferative skin diseases and immunologically-mediated diseases of the skin, such as psoriasis, psoriatic arthritis, atopic eczema
35 (atopic dermatitis), contact dermatitis and further, eczematous dermatitis, seborrhelc dermatitis, lichen planus, pemphi-
gus, bullous permphigold, epidermolysis buliosa, urticaria, angioedemas, vasculitides, erythema, cutaneous eosi-nophilias, acne, alopecla areata, eosinophilic fasciltis and atherosclerosis. The pharmaceutical composition of the present Invention can be more particularly used for hair revitalizing, such as In the treatment of female or male pattern alopecia or senile alopecia by providing epilation prevention, hair germination and/or promotion of hair generation and
40 hair growth.
[0022] The composition of the present Invention can be also used for the treatment of respiratory diseases such as
sarcoidosis, pulmonary fibrosis, idiopathic interstitial pneumonia and reversible obstructive airways disease Including conditions such as asthma including bronchial asthma, infantile asthma, allergic asthma, intrinsic asthma, extrinsic asthma and dust asthma, particularly chronic or inveterate asthma (e.g., late asthma and airway hyperresponsiveness),
45 and bronchitis and the like. The composition of the present invention can be also used for liver disorders associated with
ischemia. Moreover, it is effective for specific eye disease such as conjunctivitis, keratoconjunctivitis, keratitis, vernal conjunctivitis, uveitls associated with Behçets disease, herpetic keratitis, conical cornea, dystorphia epithelialls cor-neae, keratoleukemia, ocular pemphigus, Mooren’s ulcer, scleritis, Graves’ ophthalmopathy, severe intraocular Inflam-mation and the like.

so [0023] The composition of the present invention can be also used for the prophylaxis and treatment of inflammation
of mucosa or blood vessels such as leukotriene B4-medlated diseases, gastric ulcer, damage of blood vessel due to ischemic diseases and thrombosis, inflammatory bowel diseases (e.g., Crohn’s disease and ulcerative colitis) and necrotizing enterocolitis), and intestinal lesions associated with thermal burns. The inventive composition can be used for the prophylaxis and treatment of renal diseases such as interstitial nephrltis, Goodpasture’s syndrome, hemolytic
55 uremlc syndrome and diabetic nephropathy: neuropathy selected from multiple myositis, GulIlaIn-Barre syndrome,
Menieres disease and radiculopathy; endocrine diseases such as hyperthyroldism and Basedow’s disease; hematic diseases such as pure red cell aplasla, aplastic anemia, hypoplastic anemia, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, agranulocytosis and anerythroplasia; bone diseases such as osteoporosis; respiratory

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Comparative Example 7

[0057]

present compound 0.1%

D-mannitol 5.0%

10 polyvinylpyrrolidone 12 PF 1.0%

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[00581 The above composition Is dissolved in distilled water for Injection to give an injection having the total amount
of 10 ml.

Experimental Example 1: Hemolysis test

[0059] The preparations obtained in Examples 1 and 2 were prepared into sample solutions according to ’Yakuan
No. 2’ (Test method for topical disorder caused by injection (draft), January 12, 1979, Safety Section, Pharmaceutical
20 Affairs Bureau, Ministry of Health and Welfare) and the absorbance at 540 nm was measured according to the method
of Inglot et al., Biochem. Pharmacol. Vol. 17, p. 269 (1968). As a result, the preparations of Examples 1 and 2 were found to have significantly lower hemolytic property. In contrast, the preparations of comparative Examples 1-7 showed hemolytic property.

25 Experimental Example 2: Local irritation test

[0060] The preparation obtained in Example 1 was Intravenously repeat administered to 5-week-old LEW rats for 5
consecutive days and local irritation was confirmed using swelling ratio of the tail (diameter of tail of drug administration group - diameter of tail of control) -- diameter of tail of control x 100 as an index. As a result, the preparation of
30 Example 1 achieved 0%, showing presence of no local Irritation.

Experimental Example 3: Crystal precipitation test

[0061] The preparations obtained in Examples 1 and 2 were sterilized by filtration, filled In ampoules, melt-sealed
35 and sterilized by heating at 121°C for 20 minutes to give Injections having the total amount of 2 ml. These preparations
were left standing at room temperature for 1 week. As a result, the preparations of Examples 1 and 2 showed no pre-cipitation of crystals. The preparations of Examples 1 and 2 were left standing in a refrigerator for 1 week. Neither prep-aration showed precipitation of crystals. In contrast, the preparations of Comparative Examples 1, 2, 3, 4 and 7 showed precipitation of crystals both at room temperature and in cold storage.
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Experimental Example 4: Foaming test

[0062] The ampoules were stood erected, laid down and then stood erected, which steps were taken as one cycle.
This cycle was repeated 10 times for the preparations obtained in Examples 1 and 2. The generated foams disappeared
45 within 1 minute in the case of the preparations obtained in Examples 1 and 2, demonstrating a remarkably short
defoaming time. In contrast, the generated foams did not disappearfor at least 5 minutes In the case of the preparations
of Comparative Examples 1-7.

Industrial Applicability
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[0063] A pharmaceutical composition containing 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol or a pharma-
ceutically acceptable acid addition salt thereof, which is suitable for a liquid agent, which can be readily prepared into a pharmaceutical agent, which shows less side effects, such as hemolysis, less local irritation and superior defoaming performance, and which inhibits crystal precipitation of the active Ingredient compound, can be provided by the addition
55 of cyclodextrin as a stabilizer to 2-amino-2-[2-(4-octyiphenyl)ethyl]propane-1,3-diol or a pharmaceutically acceptable
acid addition salt thereof. incorporation of saccharide Into this composition results in an even more reduced local irrita-tion.

[0064] This application is based on application No. 8045/1998 filed in Japan, the contents of which are incorporated

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SUPERINTENDENCIA DE INDUSTRIA V COMERCIO DIRECCION DE NUEVAS CREACIONES

2020
Bogota, D.C.

Abogado
/ JIMENA ESCOBAR URIBE

ASUNTO Radicación TrÆmite
Evento
Actuaciôn
Oficio
Folios

Patente de Invenciôn

Via Nacional F I

Via PCT (fase nacional) 51

No. Sol. lnternacional
Fecha de Presentaciôn Internal

05-102278
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Patente de Modelo de Utilidad

Cap.lF-1 Cap. II
PCT/EP2004/003656
06-04-2004

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Como resultado del examen de fondo, realizado con fundamento en el articulo 45 de la Decision 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

DescripciOn:
Reivindicaciones

Prioridad:

Respuesta del solicitante:

2. Objeto de la invención

Folios 0643 como se radicO inicialmente Folios 44-45 como se radicO inicialmente Folios 126-130 como se radicO el 08-01-2009 Folios 137-142 como se radicô el 01-10-2009
Folio 1 US, 60/461.215, 08-04-2003
Folio 116-122 como se radicO el 08-01-2009

TItulo de la solicitud: COMPOSICIONES FARMACEUTICAS SOLIDAS QUE COMPRENDEN UN AGONISTA DE RECEPTOR SI P Y UN ALCOHOL DE AZUCAR (65).

3. Modificaciones no aceptadas (artIculo 34 D.486 y art. 22 Tratado PCT)

El capitulo reivindicatorlo radicado el 01-10-2009 (folios 137-142) no es aceptado porque amplia la materia del capitulo presentado el 08-01-2009 (folios 126-130) a una composiciOn que se encuentra solicitada en la solicitud divisional 05-102278A (folio 88-94), al definir que la composiciOn contiene como agonista del receptor del

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SI P el compuesto 2-amino-2-[2-(4-octilfenil)etil]propan-1,3-diol, un fosfato o una sal farmacØuticamente aceptable del mismo (folio 137; pÆg. 38).

Va que el compuesto 2-amino-2-[2-(4-octilfenil)etil]propan-1,3-diol (FTY720) es un compuesto de formula I, pero FTY720-fosfato corresponde a un compuesto de formula IVa tal como lo senala la descripciOn (folio 23; p6g.17); compuesto de formula IVa que se encuentra en las composiciones solicitadas en la divisional senalada.

4. Objeto de la invención

El problema tØcnico planteado en esta solicitud esta relacionado con la necesidad de obtener composiciones farmacØuticas sôlidas de administraciôn oral que contengan un agonista del receptor de esfingosina 1-fosfato (SP1) en baja proporción y que permitan alcanzar una uniformidad de dosis adecuada en la composiciôn (folio 8; pÆg. 2).

Para solucionar este problema tØcnico la solicitud en estudio proporciona en: Reivindicaciones 1-17: una composiciOn farmacØutica sôlida que comprende un compuesto de formula I (agonista del receptor SIP) y un alcohol de azücar.

?20R3

R4R5N CH2OR2

R1 (I)

Clasificación Internacional de Patentes (IPC): A61 K9/20, A61 K9/48, A61 K47/26, A61 31/135.

S. De la solicitud de Patente

5.1. Reivindicaciones (artIculo 30 D 486)

En la reivindicaciOn 4 la expresión "un alcohol de azücar no hiqroscôpico" no es clara ni concisa, puesto que el no ser higroscóDico es una caracteristica de un alcohol de azUcar que no lo define de manera inequlvoca; por lo tanto es necesario que se elimine el tØrmino "no higroscopico" y que dicho excipiente sea definido por su nombre genenco o qulmico acorde con las composiciones soportadas en la descripción.

En las reivindicaciones 15-16 se caracteriza inadecuadamente la composiciôn por que el activo agonista del SI P "es micronizado" y porque "es pre-tamizado con una malla dada"; no obstante, se aclara que estas no son caracterIsticas tØcnicas esenciales de la composiciôn ya que hacen referenda a caracteristicas del activo en proceso. Una composición debe ser solo caracterizada por los elementos que la comprenden como son agente activo, excipientes y sus proporciones.

Por lo anterior, el capitulo reivindicatorlo no cumple con el requisito de tener claridad y concisiOn de acuerdo con las exigencias del artIculo 30 de la DecisiOn 486.

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6. Determinaciôn del Estado de la TØcnica

Considerando que la fecha de presentación de la primera solicitud de patente es 08-04-2003, se buscaron documentos del estado de la tØcnica relacionados, con fecha de publicaciôn anterior a Østa.

N° Documento TItulo Fecha de
Publicación

D2 EPI 195165 Sphingosine-1-phosphate for treating 10-04-2002 fibrosis
Medicinal compositions containing 2-
D3 EP1050301 amino-2-[2-(4-octylphenyl)ethyl]propane- 08-11-2000
1,3-diol
Anteriondad 02 en folios 104-107 y D3 en folios 148-152.

7. Anªlisis de patentabilidad (articulo 14 D486)

4.1 Novedad (artIculo 16D486)

Se solicita en las reivindicaciones 1-6 y 8-10, una composición farmacØutica sôlida que comprende un compuesto de formula I (agonista del receptor SI P) y un alcohol de azUcar (como manitol), donde el activo puede estar entre (0,01 -20) % y ademÆs puede contener un agente lubricante.

Al comparar elemento por elemento el objeto de la presente solicitud con el estado de la tØcnica, se encuentra que:

D3 divulga composiciones que comprenden el compuesto 2-amino-2-[2-(4-octilfenil)etil]propan-I,3-diol (un compuesto de formula / de Ia solicitud) y manitol, conteniendo entre (1,6-2)% del activo y conteniendo opcionalmente laurilsulfato de sodio, polisorbato 80, aceite vegetal hidrogenado polivinilpirrolidona (folios 151-152; pÆg.8-9, ej. 3-7).

En consecuencia, las composiciones reveladas en D3 y que se encuentran en el alcance de la solicitud no son nuevas.

4.2 Nivel inventivo (artIculo 18 D486)

Adicional a la materia seæalada en el numeral de novedad, se solicita en las reivindicaciones 7 y 11-17 la composiciôn en donde el lubricante es estearato de magnesio, el lubricante estÆ entre(0,01-5) % y el alcohol de azücar estÆ entre el (90-99,5) %.

El estado de la tØcnica mÆs cercano es D3 que divulga composiciones que comprenden el compuesto 2-amino-2-[2-(4-octilfenil)etil]propan-I, 3-diol (un compuesto de formula I de Ia solicitud) y manitol, conteniendo entre (1,6-2)% del activo y conteniendo opcionalmente laurilsulfato de sodlo, polisorbafo 80,iceite vegetal hidrogenado polivinilpirrolidona (folios 151-152; pÆg. 8-9, ej. 3-7); igualmente indica que el activo puede estar entre (0,01-20)%, que el alcohol de azücar puede estar entre I a 100 partes por partØ en peso del activo y que la composiciOn puede ser solida como un polvo liofihizado (folio 149-150; pÆg.3-4).

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De manera que la solicitud se diferencia de D3 en que seæalaespecificamente que el manitol se encuentra entre el (90-99,5) % y que el lubricante estearato de magnesio se encuentra entre (0,01-5) % en la composiciôn.

El efecto tØcnico que logra tal diferencia es obtener una composición sólida uniforme con una proporciOn baja del activo agonista del receptor SI P (folio 8; pÆg.2).

AsI que, el problema tØcnico objetivo de la solicitud es lograr una composiciôn farmacØutica solida con baja proporciôn de un agonista del receptor SI P, que tenga uniformidad de dosis.

Sin embargo, se aclara primero que para un experto en la materia aumentar la proporcion de manitol no es inesperado puesto que es comünmente reconocido que es posible usar altas proporciones de manitol que es un diluente preferido gracias a sus buenas caracterIsticas de flujo, compresibilidad, bajo contenido de humedad y estabilidad en estado solido (Handbook of pharmaceutical Excipients, 2000, folios 144-147), lo que incluso confirma 03 al indicar que el alcohol de azücar puede estar entre I a 100 partes por parte en peso del activo.

Y segundo, que utilizar estearato de magnesio como lubricante en la proporciôn seæalada tambiØn es comünmente conocido por un experto en la materia como 10 ejemplifica D2 al seæalar que un compuesto agonista delreceptor de esfingosina I-fosfato (SI P) puede ser administrado en formas sôlidas, en donde el agente activo pueden ser mezclados con un vehIculo como manitol y un lubricante como estearato de magnesio (folio 105, 107; pÆg. 3, 5).

Por consiguiente, para un experto en la materia teniendo en cuenta la información de D2 y D3, la composiciôn reivindicada no tiene nivel inventivo.

8. Respuesta al solicitante

El solicitante realiza una solicitud divisional, la cual es aceptada puesto que la materia solicitada en el nuevo capitulo de la solicitud original (folios 126-130) es diferente a la materia que se solicita en la divisional 05-102278A (folio 88-94) ya que el agente activo de la composiciôn es diferente en cada solicitud.

> En cuanto a novedad el solicitante senala que Dl ya no afecta la novedad de la
solicitud puesto que los compuestos divulgados alli ya no se encuentran dentro de las composiciones ahora solicitadas (folio 119; pÆg.4 de respuesta).

En relaciôn con lo anterior, se observa que efectivamente composiciones con un compuesto de formula II (divulgados en Dl) ya no son solicitadas, por lo que Dl ya no afecta la novedad.

> En relaciôn con el nivel inventivo, el solicitante senala que DI y 02 no afectan la
materia ahora solicitada puesto que DI y D2 divulgan de manera general los excipientes mezclados con un agonista de SI P (diferentes al de la solicitud) en una composición (folios 120-121; pag. 5-6 de respuesta).

Al respecto, se observa que los agonistas de SIP Dl y 02 son diferentes a los que se incluyen en las composiciones ahora solicitadas; por lo que el nivel inventivo estä ahora afectado por D3 y D2 para un experto en la materia, tal como se explica en el respectivo numeral.

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9. Conclusion

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados asi:

N° Documento N° Reivindicaciones Requisito quo Afecta Afectadas
D2 EP1195165 7yI1-17 Nivelinventivo

1-6 8-10 Novedad D3 EP1050301 7 11-17 Nivel inventivo

En cumplimiento del artIculo 45 de la Decision 486 de la ComisiOn de la Comunidad Andina, se le indica que debe dar respuesta dentro del tØrmino de sesenta dias contados a partir de Ia fecha de notificaciOn de la presente comunicaciOn. En caso de no dar respuesta al presente requerimiento, 0 SI a pesar de la respuesta subsistieran los impedimentos para la concesiOn, se denegara la patente.

Notifiquese el presente oficio conforme a lo dispuesto en el articulo 8 de la resoluciOn reglamentaria No. 00210 del 15 de enero de 2001, advirtiendo que contra Øl no procede recurso alguno ep, la via gubernativa.

ALIX CARMEN,ZA CESPEDES DE VERGEL
Directora de Fs}(ievas Creaciones (C)

El anterior requerimiento fue notificado por fijaciOn en lista, de fecha 5

CONCEPTO TECNICO EXAMINADOR TECNICO
No. 269 COdigo No. 202079

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EXAMEN TECNICO DE FONDO
N° RadicaciOn 05-102278 Fecha de presentaciOn 07-10-2005
N° Solicitud Intemacional PCTIEP2004/003656 Fecha Solicitud Intemacional 06-04-2004
N° Prioridad US, 60/461.215, Fecha de Prioridad 08-04-2003

Palabras dave compositions containing 2-amino-2-[244.
octylphenyI)ethyl]propane-1,3-dIol and manitol SPI agonist compositions
Inventor; TOMOYUKI OOMURA, MADHUSUDRAN
PUDIPEDDI, ALAN EDWARD ROYCE, COLLEEN
RUEGGER,
MASAKI SASAKI, TOKUHIRO TAMURA.

2-amino-2-[244-octilfenil)eUu]propano-
1,3-did

I2-amino-2(244(1 -oxo-7-
Iphenyl)ethyl)propane-1,3-diol

2-aniinopropane-1,3-diol compounds

agonista del recpetor do fosfato de
esfingosina -1. Compuestos
inmunomoduladores

Solicitante: NOVARTIS AG Ispi agonist compositions and manitol

CLASIFICACIONIES IWTERNAC1ONALES DE BUSQUEDA

A61 K 9/20, A61 K 9/48, A61 K47126, A61 K 31 /- 5

DOCUMENTOS CORRESPONDIENTES EN OTROS PAISES
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